The Association of Anthropometrics, Adipokines and Body Fat Distribution with Morning Serum Cortisol in African Americans: Jackson Heart Study

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Short Title: Anthropometrics, Adipokines, Body Fat and Cortisol in African Americans

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Abstract:

Background:

Altered hormonal regulation, including cortisol, is a proposed mechanism linking adiposity to obesity-related disorders. African Americans (AAs) have differences in body fat distribution compared to whites including less visceral and more subcutaneous fat, which may be reflected in the association of cortisol with adiposity. We examined the association of anthropometric, adipokine and body fat distribution measures of adiposity with morning serum cortisol (cortisol) in an AA cohort, the Jackson Heart Study.

Methods:

We examined the cross-sectional associations of adiposity measures (body mass index [BMI], waist circumference [WC], leptin, adiponectin, leptin:adiponectin ratio [LAR], subcutaneous [SAT] and visceral adipose tissue [VAT], and liver fat with cortisol. Leptin, adiponectin, LAR, cortisol, SAT, VAT, and liver fat were log-transformed and standardized (z-scores) prior to analysis due to positively skewed distributions. Linear regression models were used to analyze the association between exposures and cortisol. Models were adjusted for age, sex, education, occupation, systolic blood pressure, smoking, physical activity, hormone replacement therapy, β-blocker medication, and time of cortisol collection.

Results:

Among 4,211 participants, a 1-SD higher BMI, WC, leptin, leptin:adiponectin ratio, SAT were associated with a 3.92%, 3.05%, 6.48%, 4.97% and 4.97% lower cortisol (all $p < 0.001$). A 1-SD higher adiponectin was associated with a 2.33% higher cortisol ($p<0.001$). Leptin levels in the 2^{nd} - 4^{th} quartiles were associated with a graded 7.6%, 11.6%, 15.5% lower cortisol, respectively (all $p<0.0001$). Compared to normal BMI, overweight BMI (25-29.99 kg/m2) and obese BMI (≥

30 kg/m2) were associated with a graded 7.7% and 13.2% lower cortisol, respectively (both p<0.0001). There were no associations of liver fat or VAT with cortisol.

Conclusion:

Several measures of adiposity are associated with lower morning serum cortisol among AAs with leptin having the greatest magnitude. Future studies examining the role of morning serum cortisol in the pathway from adiposity to cardiometabolic disease in AAs are warranted.

Keywords: Adiposity, Body Mass Index, Body Fat Distribution, Adipokines, Cortisol, African Americans

INTRODUCTION:

Obesity impacts nearly 1 in 2 African Americans (AAs) in the United States (US) (1). Visceral adipose tissue (VAT) actively secretes pro-inflammatory cytokines and is associated with an increased risk of coronary artery disease (2, 3)). Interestingly, AAs have less VAT and more subcutaneous adipose tissue (SAT) compared to non-Hispanic whites (NHWs) and other racial/ethnic groups (4, 5). Despite having a lower burden of VAT, AAs have a significantly higher prevalence of cardiovascular disease (CVD) than NHWs (6). This discrepancy suggests that adiposity may drive cardiometabolic disease through factors independent of visceral adiposity in AAs. Thus, there is a need to explore novel risk factors that are influenced by adiposity and are known to increase CVD risk. One such risk factor is cortisol, whose excess and dysregulation with respect to normal circadian patterns is associated with cardiometabolic disease and mortality (7, 8).

Perturbations of the hypothalamic-pituitary-adrenal (HPA) axis and cortisol have been cross-sectionally associated with obesity (BMI>30 kg/m2) and obesity related conditions including insulin resistance, type 2 diabetes, metabolic syndrome and CVD (9, 10). A meta-analysis of smaller studies reported mixed associations between adiposity and morning blood cortisol; however, larger studies have found significant negative associations between anthropometric measures of adiposity and serum/plasma cortisol in Caucasian individuals (11–13). Higher BMIs and greater waist circumferences are consistently associated with lower salivary wake-up cortisol and cortisol awakening responses (14, 15). Additionally, a U-shaped relationship between adiposity and morning serum cortisol has been identified (16). With the exception of one study (14), these associations have been investigated in predominantly non-Hispanic white and European individuals. Among community dwelling individuals, longitudinal studies suggest that changes in adiposity drive perturbation of the HPA axis and cortisol production (17, 18).

These studies suggest that temporality favors changes in adiposity preceding alterations in systemic cortisol production.

Previous studies have been limited to anthropometric assessments of adiposity (BMI, WC, waist-to-hip ratio) and lacked the ability to examine more specific measures of adiposity including adipokines and body fat distribution in association with cortisol in large populations. Furthermore, previous studies have suffered from a lack of racial/ethnic diversity or power to perform race stratified analyses. Given that significant racial/ethnic differences exist in adipose tissue distribution (4, 5), we examined the association between measures of adiposity and morning serum cortisol in African Americans in the Jackson Heart Study. We hypothesized that anthropometric (waist circumference, BMI), adipokines (leptin, leptin: adiponectin ratio [LAR]) and body fat distribution (VAT, SAT, Liver Fat) measures of adiposity would be negatively associated, while adiponectin would be positively associated with morning serum cortisol.

METHODS:

Study Population:

The Jackson Heart Study (JHS) is a prospective cohort study of 5,306 African American adults, aged 21-94 from the tri-county area of metropolitan Jackson, Mississippi. The Initial examination of participants was performed between 2000-2004 and they were followed-up twice between 2005-2008 and 2009-2013. The design of the JHS has been described elsewhere (19). The study was approved by the institutional review boards of the University of Mississippi Medical Center, Jackson State University, and Tougaloo College. All participants provided informed consent. Participants were excluded if they had missing data on exposures (morning serum cortisol [n=113]), outcomes (adiponectin [n=91], leptin [n=21], waist circumference [n=6], BMI [n=1 exam 1], or important covariates at the initial exam (education [n=23], systolic blood

pressure [n=15], smoking [n=38], diabetes status [n=4], beta-blockers [n=381]), and cortisol measuring time missing or after 12 pm [n=402] (Figure 1).

Assessment of Adiposity Measures:

WC was measured at the level of the umbilicus in centimeters (cm) and BMI was calculated as weight, in kilograms (kg), divided by height, in meters (m), squared. Visceral and subcutaneous adipose tissue volume as well as liver attenuation were measured via multidetector computed tomography (CT). The protocol for CT assessment of adiposity in the JHS has been previously described (20). Briefly, a 16-channel multidetector CT system equipped with cardiac gating (Lightspeed 16 Pro; GE Healthcare, Milwaukee, WI) scanned the heart and lower abdomen. Quality control and image analysis were performed at a core reading center (Wake Forest University School of Medicine, Winston-Salem, NC). VAT and SAT were assessed from abdominal imaging slices covering the lower abdomen from L3 to S1. In total, 24 contiguous 2-mm-thick slices centered on the lumbar disk space at L4–L5 were used for this analysis; 12 images before the center of the L4–L5 disk space and 12 images after the disk space were used for quantification of VAT and SAT. The abdominal muscular wall was first manually traced, and the fat volumes in different compartments were measured by semiautomatic segmentation technique. Volume analysis software (Advantage Windows; GE Healthcare, Waukesha, WI) was used to segment and characterize each individual voxel as a tissue attenuation of fat using a threshold range of −190 to −30 Hounsfield units (HU). The VAT and SAT volumes were the sum of VAT and SAT voxels over 24 slices. A CT diagnosis of fat infiltration in the liver was made by measurement of liver attenuation (LA) in HU in the right lobe of the liver at the T12-L1 intervertebral space. As liver fat increases, the measured LA decreases based on the HU in which fat has negative values. The LA was determined by calculating the mean Hus of three circular regions of interest measuring 100 mm^2 in the parenchyma of the right lobe of the liver. Given that CT measures were collected at Exam 2, we tested for change in adiposity between

Exam 1 and 2 (median 4 years). To determine the variance of adiposity levels in the time between Exams 1 and 2, the intraclass correlation coefficients (ICC) were analyzed for BMI, WC, and WHR. The ICC for BMI, WC, and WHR was 0.90, 0.83, and 0.83 respectively. The intraclass correlations were greater than 80%, suggesting adiposity was consistent between visits. Thus, CT measures were included in cross-sectional analyses.

Assessment of Adipokines:

Leptin and adiponectin were assessed using venous blood which was collected after a minimum of 8 hours of fasting and 20 minutes in the supine position. Blood samples were processed using a standardized protocol and were stored at -80°C before serum adiponectin and leptin was measured (19). Total adiponectin concentration was measured using an ELISA system (R&D Systems; Minneapolis, MN, USA). The inter-assay coefficient of variation was 8.8% (21). Leptin was measured with a Human Leptin RIA kit (LINCO Research, St. Charles, MI, USA). Coefficients of variation was 10% (22). The leptin:adiponectin ratio was calculated via division of leptin by adiponectin.

Assessment of Morning Serum Cortisol:

Normal diurnal cortisol regulation follows a circadian pattern, in which levels are typically high upon waking, rise during the first 30–40 minute post-awakening and decline across the day, reaching a nadir in the late evening around 11pm-midnight (23). In the JHS, fasting serum cortisol was collected in the morning between 8am and 12 pm. Serum cortisol levels were measured by chemiluminescent immunoassay performed on an immunoassay system (ADVIA Centaur; Siemens). Intra-assay coefficients of variation were 9.1% and 7.7% for high and low cortisol concentrations, respectively.

Assessment of Covariates:

Information regarding covariates was obtained at the baseline exam. Data were collected during visits to the clinic or at home using questionnaires designed to assess occupation (management/professional versus not), educational attainment (less than high school versus high school diploma/GED equivalent), smoking status (current smoking versus not), medical conditions and medication use (beta-blocker/hormone replacement therapy). Systolic blood pressure was taken while seated and was measured twice in 5-minute intervals. The average of the two measurements was used for the analysis. Physical activity was categorized according to the AHA 2020 Cardiovascular health guidelines as poor, intermediate, or ideal, as described previously (24).

Statistical Analyses:

Baseline characteristics of participants were presented and compared across tertiles of BMI using analysis of variance (ANOVA) for parametric continuous variables, the Kruskal-Wallis test for non-parametric continuous variables, and the chi-square test for categorical variables. Due to skewed distributions, cortisol, adiponectin, leptin, LAR, SAT, VAT, and liver fat measures were log-transformed prior to the analysis. We used multivariable linear regression models to assess the association between anthropometric (BMI & WC), CT (VAT, SAT, & Liver Fat), and biomarker (Adiponectin, Leptin, & LAR) measures of adiposity after testing for a non-linear association between measures of adiposity and log-morning serum cortisol (Supplementary Figure 1). Relative magnitudes of associations between exposures and morning serum cortisol were assessed by standardizing each exposure variable. Various demographic, socioeconomic, and biological factors which have previously been shown to be associated with the exposure, outcome, or both were controlled for in the model. Both age and male sex are consistently associated with higher total daily cortisol output (25, 26). Higher levels of education are associated with greater wake up cortisol levels and higher total daily output across the day among AAs (27). Higher socioeconomic status, a proxy for both greater occupational and

educational attainment, is associated with a lower wake up cortisol (28). Individuals who actively smoke have higher total cortisol output throughout the day (29). Systolic blood pressure is well known to increase with adiposity and may be a proxy for increased sympathetic nervous system activity (30). Beta-blocker medications have significant interactions with the HPA-axis. Estrogen monotherapy increases circulating plasma cortisol while an estrogen and progestin combination shows a trend towards increasing cortisol (31). Furthermore, HRT influences body composition in post-menopausal women (32). Finally, due to the circadian nature of cortisol output, we controlled for time of cortisol collection. Effect modification was tested by age and sex by inserting multiplicative interaction terms in the models and using the likelihood ratio test. Statistical significance was defined as two-sided alpha <0.05 in the main analysis and <0.10 for interactions (33). Analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS:

Among 4,211 participants, the majority were female (64%), had a level of education equivalent to or greater than a high school diploma (81%), were non-smokers (87%), and did not have diabetes (79%). The average participant was 54.9 years old (SD: 12.7), had a BMI of 31.7 kg/m^2 (SD: 7.2), and a waist circumference of 100.6 cm (SD: 16.2). Participants in higher tertiles of BMI were significantly less likely to smoke, had lower levels of morning serum cortisol, a greater prevalence of diabetes, and higher systolic blood pressures. Individuals in higher categories of BMI had lower adiponectin and liver attenuation as well as higher leptin, SAT, and VAT (Table 1).

Examining the continuous relationships between adiposity measures and cortisol (Table 2), a 1% higher adiponectin was found to be associated with a 0.034% higher morning serum cortisol. A 1% higher leptin and LAR were associated with 0.07% and 0.045% lower cortisol, respectively, in the fully adjusted models (both $p<0.001$). A 1 kg/m^2 higher BMI and 1 cm higher

WC were associated with 0.6% and 0.2% lower cortisol, respectfully (both p<0.0001). A 1% higher SAT was associated with a 0.1% lower morning serum cortisol in the fully adjusted model (p<0.0001). No associations were observed between visceral adipose tissue and liver attenuation with baseline cortisol.

A 1-SD unit increase in leptin was associated with a 6.48% (β= -0.067, CI: -0.084, -0.05, p<0.0001) lower morning serum cortisol and a 1-SD higher adiponectin was associated with a 2.33% (β= 0.023, CI: 0.01, 0.036, p=0.0005) higher morning serum cortisol. Both a 1-SD unit increase in LAR and SAT were associated with a 4.97% (LAR [β= -0.051, CI -0.065, -0.038, <.0001] & SAT [β= -0.051, CI, -0.07, -0.032, <.0001]) lower morning serum cortisol. A 1-SD higher WC and BMI were associated with a 3.05% (β= -0.031, CI: -0.043, -0.018) and 3.92% (β= -0.04, CI: -0.052, -0.027) lower morning serum cortisol (both p<0.0001, Table 3, Figure 3).

In the categorical analysis (Table 4), adiponectin in quartile 4 was associated with a 5.7% higher cortisol than quartile 1 with no evidence for a graded association. Leptin in the 2nd, 3rd, and 4th quartiles was associated with 7.6%, 11.6%, 15.5% lower cortisol (respectively) compared to the 1st quartile. Increasing quartiles of the LAR and waist circumference were also associated with lower morning serum cortisol. Compared to normal BMI, overweight and obese BMI was associated with a 7.7% and 13.2% lower cortisol, respectively. SAT in the 3rd and 4th quartiles were associated with a 10.1% and 10.0% lower cortisol, respectively (all p<0.05). No significant associations were identified in the fully adjusted models assessing the association of VAT and liver attenuation with cortisol.

No consistent effect modification was identified by age and sex. Additionally, there was no evidence of a U-shaped association between measures of adiposity and morning serum cortisol (Supplementary Figure 1a-d).

DISCUSSION:

In a large sample of AAs, we examined the association of adiposity measures, including anthropometric, adipokine and body fat distribution with morning serum cortisol. In this study, leptin, LAR, BMI, WC, and SAT were negatively associated while adiponectin was positively associated with morning serum cortisol. Leptin had the greatest magnitude of relative association with morning serum cortisol in standardized analyses.

Anthropometric Measures

Previous studies have investigated the cross-sectional relationship between anthropometric adiposity measures and cortisol; however, to our knowledge, this is the first to examine these associations in a large cohort of AAs and, more generally, with objective measures of adiposity including adipokines and CT measures of body fat distribution. Concordant with our study, BMI, WC, and hip circumference had significant negative correlations with morning serum cortisol, among middle-aged Scandinavian men (11) and middle-aged white men (34). While there was no evidence of effect modification by sex in the JHS, differences in the association between adiposity and cortisol have previously been identified between men and women in other populations. In a larger Scandinavian cohort, fasting cortisol was negatively correlated with measures of central adiposity in women, but not in men (13). Similarly, body weight and mean 24-hour plasma cortisol are inversely correlated among women; however, the two are invariant in men (35). The lack of sex specific differences may be related to the high degree of generalized and abdominal obesity in the JHS compared to other previous studies and the detailed phenotypic biological and imaging characterizations used in this study.

Some prior studies are discordant with those aforementioned having identified non-linear relationships between obesity and morning serum cortisol among whites.. A U-shaped association between BMI and morning serum cortisol has been identified with cortisol nadiring at a BMI of 32 among white women (16). However, another study identified a linear association of BMI with cortisol (15). In the current study, there was no evidence of a U-shaped association between either BMI or WC and morning serum cortisol. This may be due to the distribution of BMI in the JHS with only 14% of the participants having a BMI < 25 and mean BMI of 22.7 kg/m^2 among those participants. One potential hypothesis that may explain the previously identified U-shaped association is that the state of "underweight" may drive HPA axis activation and cortisol output. In the current sample, very few participants had a BMI < 18 kg/m^2, which may have hindered our ability to detect a significant signal.

Studies examining the association between adiposity and free salivary cortisol show similar results to those assessing plasma and serum cortisol. In the Whitehall II cohort, a linear trend between increasing categories of BMI (underweight, normal, overweight, and obese) and lower wake-up cortisol as well as blunted cortisol awakening responses was reported. These associations were mirrored with WC as the exposure (15). While the majority of investigations examining these associations were in Caucasian participants, an analysis in the Multi-Ethnic Study of Atherosclerosis (MESA) reported similar findings, but were limited in power for racial/ethnic stratifications (14).

The hypothesized temporality of the associations between BMI and WC with altered HPA-axis function is that adiposity precedes perturbations of the glucocorticoid-regulating system. This hypothesis is based on work in MESA where investigators found that a 1% higher annual change in BMI was associated with a 2.9% lower wake-up and 3.1% lower 16-hour AUC

salivary cortisol over a seven year period (17). Similar associations were reported with waist circumference as the exposure. These findings are corroborated by the Massachusetts Male Aging Study (18). Although the current study is cross-sectional, it is consistent with these previous findings as we found negative cross-sectional associations between continuous measures of both BMI and WC with morning serum cortisol.

The specific site of adipose tissue deposition has also been examined as a potential modulating factor of morning cortisol levels. In a comparison of abdominally versus peripherally obese women, those with abdominal body fat distributions had significantly lower wake-up cortisol and cortisol awakening responses than those with peripheral body fat distributions (36). This study, however, used less sophisticated measures of adipose tissue distributions than those used in the JHS. In the current study, SAT was associated with significantly lower morning serum cortisol while VAT and liver fat were unrelated to morning cortisol. Previously, a U-shaped relationship between VAT and morning serum cortisol was identified in women (16). Testing for a non-linear association between both visceral and liver fat in the JHS revealed no significant findings (Supplementary Figure 1c & 1d). VAT and liver fat may be associated to a greater degree with local cortisol production, regulated by 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), which may not be reflected in changes to circulating levels.

Body Fat Distribution

Although, VAT is generally considered a greater component for CVD risk due to its pro-inflammatory effects, SAT is also cross-sectionally associated with cardiometabolic risk factors (37). Given that AAs have the highest rates of obesity in the US, the absolute magnitude of SAT may play a larger role in CVD burden than the relative ratio of VAT to SAT. While VAT directly secretes IL-6 into circulation, SAT upregulates TNF-α indirectly through leptin production which contributes to systemic inflammation (2, 38). In addition to their relationship with systemic

inflammation, the current analysis suggests that SAT and leptin are associated with HPA-axis dysfunction which may ultimately manifest itself in cardiometabolic disease (Figure 2). As previously articulated, lower levels of cortisol in the morning are generally considered indicative of HPA-axis dysfunction. Further research is needed to explore cortisol as a potential mediator of the relationship between SAT driven adiposity with cardiometabolic disease among AAs.

Adipokines

To our knowledge, this is the first study to examine the association between leptin and cortisol in a large AA cohort. Leptin, is considered the primary peripheral protein involved in appetite regulation and exerts its effects largely through the hypothalamus (39). Circulating levels of leptin have a strong positive correlation with overall fat mass as it is secreted primarily by subcutaneous adipose tissue (40). Interestingly, leptin and cortisol share an inverse circadian rhythm which is suggestive of potential counter-regulation (41). In support of this relationship, leptin is able to directly suppress the activity of the HPA-axis at the hypothalamus as it blunts the release of corticotropin releasing hormone (CRH) in response to hypoglycemic stress (42). Additionally, incubation of adrenocortical cells with leptin inhibits both basal and adrenocorticotropin hormone (ACTH) stimulated cortisol release, further linking leptin to attenuated systemic cortisol production (43, 44). Two previous investigations have examined the relationship between leptin as the exposure and cortisol as the outcome. In one study of 11 healthy young men evaluating the influence of sleep duration on various biomarkers including 24-hour measures of leptin and cortisol, where researchers found an inverse relationship throughout the daytime (41). In the other, leptin did not significantly correlate with cortisol among middle-aged Scandinavian men (11). In the current study, the negative association between leptin and morning serum cortisol may explain the relationship observed with SAT as the exposure. SAT was negatively associated with morning serum cortisol in the continuous model. Given the ability of leptin to suppress the activation of the HPA-axis at the hypothalamus

and cortisol production at the adrenal gland, the association may be explained through this shared molecular physiology.

Adiponectin, the most abundant adipokine in circulation, increases insulin sensitivity, is an anti-inflammatory protein, and is protective against cardiovascular disease (45). It is exclusively produced by adipocytes and decreases as adipocytes expand, thus is inversely correlated with BMI, body fat percentage, waist circumference, as well as VAT and SAT (46). Consistent with our findings in a small study of Caucasian men and women, those with adiponectin levels in the fourth quartile had significantly higher morning serum cortisol levels than those in lower quartiles of adiponectin (47).

To our knowledge, this is also the first investigation to examine the association between the LAR and cortisol. The LAR may be a potential surrogate measure estimating adipose tissue dysfunction (48). Increasing fat cell size is associated with lower adiponectin expression and is secreted to a greater degree by SAT (49–51). Furthermore, leptin is also primarily expressed by SAT (40). This suggests that the LAR may have more specificity for SAT dysfunction. Interestingly, the standardized LAR and SAT had the same relative magnitude of effect on morning serum cortisol. The degree of HPA-axis suppression in the morning may thus be a function of the magnitude of subcutaneous adipocyte dysfunction.

Our study has several strengths. First, our study uses data from the JHS, which has a large sample of AAs, a population who prior had limited data on the relationship between HPA-axis dysfunction and measures of adiposity. Next, we were able to assess tissue specific depots of adiposity via CT scans of visceral, subcutaneous, and liver fat. Furthermore, we were able to assess levels of important adipokines among study participants, thus, giving a greater insight into the role of adiposity on potential biochemical links to the HPA-axis. However, this

investigation should be interpreted in the light of some limitations. First, given the cross-sectional nature of the study, the temporality between the associations cannot be determined. Second, we were limited by a single measure of morning serum cortisol, and thus, were unable to assess the diurnal cortisol profile and its relation to the exposure. Third, the JHS is a single-site study, which precludes the results from being generalizable to AAs throughout the US. Lastly, though the strength of this study is to allow greater understanding of CVD in AAs, our work lays the foundation for future studies to further explore the disparities between AAs and other racial groups in adiposity, hormonal and adipokine dysregulation, and CVD.

CONCLUSION:

In conclusion, this is the first study to examine the association between anthropometric, adipokine, and body fat distribution with morning serum cortisol in a large group of AAs. Leptin, LAR, BMI, WC, and SAT were negatively associated with morning serum cortisol, while adiponectin had a positive association with cortisol. The strongest relative association was found between leptin and cortisol. AAs have the highest rates of obesity in the US and preferentially store adipose tissue in SAT. Leptin is primarily produced from SAT and is able to suppress HPA-axis activity leading to potential long-term dysfunction of the system. Thus, the interactions between adiposity, leptin, and cortisol axis warrant further investigation among AAs for cardiometabolic disease prevention.

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Table 1: Demographic Summary by Body Mass Index Categories

Characteristic	**Level**	**<25 kg/m^2 (n=596)**	**25-30 kg/m^2 (n=1373)**	**30+ kg/m^2 (n=2242)**	**Total (n=4211)**	**p-value**
Age (years)	Mean (SD)	54.5 (14.5)	56.3 (12.6)	54.2 (12.2)	54.9 (12.7)	<.0001
Sex	Female	320 (54%)	762 (55%)	1626 (73%)	2708 (64%)	<.0001
	Male	276 (46%)	611 (45%)	616 (27%)	1503 (36%)	
Education	< high school	124 (21%)	265 (19%)	432 (19%)	821 (19%)	0.6844
	high school >	472 (79%)	1108 (81%)	1810 (81%)	3390 (81%)	
Occupation	Management/ Professional	207 (35%)	524 (38%)	774 (35%)	1505 (36%)	0.0734
	other	389 (65%)	849 (62%)	1468 (65%)	2706 (64%)	
Physical Activity LS7 Category	Poor Health	300 (50%)	611 (45%)	1135 (51%)	2046 (49%)	<.0001
	Intermediate Health	183 (31%)	427 (31%)	712 (32%)	1322 (31%)	
	Ideal Health	113 (19%)	335 (24%)	395 (18%)	843 (20%)	
Current Smoking	No	458 (77%)	1198 (87%)	2011 (90%)	3667 (87%)	<.0001
	Yes	138 (23%)	175 (13%)	231 (10%)	544 (13%)	
Systolic blood pressure (mmHg)	Mean (SD) (min, max)	125.7 (17.3) (88.1, 188)	126.5 (16.5) (78, 199)	127.9 (16.1) (88.1, 228.4)	127.2 (16.4) (78, 228.4)	0.0028
Diastolic Blood Pressure (mmHg)	Mean (SD) (min, max)	75.5 (9) (50.1, 110.7)	75.6 (8.5) (48.5, 110.7)	76.1 (8.6) (36, 112.4)	75.8 (8.6) (36, 112.4)	0.1849
Body Mass Index (kg/m^2)	Mean (SD) (min, max)	22.7 (1.9) (14.6, 24.9)	27.6 (1.4) (25, 29.9)	36.7 (6.1) (30, 75.1)	31.7 (7.2) (14.6, 75.1)	<.0001
Waist Circumference (cm)	Mean (SD) (min, max)	81.8 (8.1) (60, 114)	92.8 (8.1) (32, 134)	110.4 (14.4) (66, 244)	100.6 (16.2) (32, 244)	<.0001
Waist-Hip Ratio	Mean (SD) (min, max)	0.5 (0) (0.4, 0.7)	0.5 (0) (0.2, 0.8)	0.7 (0.1) (0.4, 1.3)	0.6 (0.1) (0.2, 1.3)	<.0001
Adiponectin* (ng/dL)	Mean (SD) (min, max)	8.6 (0.7) (6.1, 10.9)	8.4 (0.7) (5.9, 11)	8.3 (0.7) (5.9, 10.6)	8.3 (0.7) (5.9, 11)	<.0001
Leptin* (ng/dL)	Mean (SD) (min, max)	2 (0.9) (-0.1, 3.9)	2.6 (0.8) (0.2, 4.5)	3.5 (0.7) (0.5, 5.9)	3 (1) (-0.1, 5.9)	<.0001
SAT (cm^3)*	Mean (SD) (min, max)	missing=2867 (0.6) (3.4, 8.1)	missing=568 7.4 (0.3) (4.8, 8.3)	missing=1017 7.9 (0.3) (6.2, 8.6)	missing=1871 7.6 (0.5) (3.4, 8.6)	<.0001

VAT (cm^3)*	Mean (SD) (min, max)	missing=286 6.1 (0.6) (4.2, 7.3)	missing=568 6.5 (0.5) (4.4, 7.6)	missing=1016 6.8 (0.4) (4.5, 7.9)	missing=1870 6.6 (0.5) (4.2, 7.9)	<.0001
Liver Attenuation HU*	Mean (SD) (min, max)	missing=278 4.1 (0.1) (3.1, 4.5)	missing=557 4.1 (0.2) (1.8, 4.4)	missing=989 4 (0.2) (2.3, 4.6)	missing=1824 4.1 (0.2) (1.8, 4.6)	<.0001
Morning Serum Cortisol* (µg/dL)	Mean (SD) (min, max)	2.3 (0.4) (0.6, 3.6)	2.2 (0.4) (-0.9, 3.5)	2.1 (0.4) (-0.9, 3.6)	2.2 (0.4) (-0.9, 3.6)	<.0001
HRT Medication	No	516 (87%)	1183 (86%)	1876 (84%)	3575 (85%)	0.0598
	Yes	36 (6%)	141 (10%)	251 (11%)	428 (10%)	
Beta Blocker Medication	No	560 (94%)	1232 (90%)	1991 (89%)	3783 (90%)	0.0010
	Yes	36 (6%)	141 (10%)	251 (11%)	428 (10%)	

*Indicates Logged Value

Legend:

LS7 = Life's Simple Seven; ideal, intermediate, and poor were defined by American Heart Association (AHA) "2020" Guidelines; SAT = Subcutaneous Adipose Tissue; VAT = Visceral Adipose Tissue; HU = Hounsfield Units; HRT = Hormone Replacement Therapy.

p-values calculated using chi-square (categorical variables), ANOVA (parametric continuous variables, and Kruskal-Wallis test (non-parametric continuous variables).

Table 2. Association of Continuous Anthropometric, Adipokines and Body Fat Distribution with Cortisol

Measures of Adiposity	Cortisol * (N=4211)
	Beta (CI), p-value
Adiponectin (ng/dL)*	0.034 (0.015, 0.053), 0.0005
Leptin (ng/dL)*	-0.07 (-0.088, -0.052), <.0001
Leptin: Adiponectin Ratio (LAR)*	-0.045 (-0.058, -0.033), <.0001
Waist circumference (cm)	-0.002 (-0.003, -0.001), <.0001
BMI (kg/m^2)	-0.006 (-0.007, -0.004), <.0001
Subcutaneous Adipose Tissue (cm^3)* (N=2340)	-0.1 (-0.14, -0.06), <.0001
Visceral Adipose Tissue (cm^3)* (N=2341)	-0.014 (-0.048, 0.02), 0.4271
Liver attenuation (Hounsfield units)* (n=2387)	0.029 (-0.054, 0.112), 0.4988

*Indicates Logged Value

1. Unadjusted model
2. Adjusted for age, sex, education, occupation, systolic blood pressure, smoking, physical activity, hormone replacement therapy medications, beta-blocker medications and cortisol collect time.

Logged-dependent variable, level-independent: $\%\Delta Y = \left(e^{\beta} - 1\right) * 100$
Logged-dependent variable, logged-independent: $\%\Delta Y = (1.01^{\beta} - 1) * 100\%$

Interpretations: A 1% higher adiponectin is associated with a 0.034% higher morning serum cortisol. A 1% higher leptin is associated with 0.07% lower morning serum cortisol. A 1% higher leptin: adiponectin ratio is associated with 0.045% lower cortisol. A 1 kg/m^2 higher BMI is associated with a 0.6% lower cortisol. A 1 cm higher WC is associated with a 0.2% lower cortisol. A 1% higher SAT was associated with a 0.1% lower morning serum cortisol.

Table 3. Association of Standardized Continuous Anthropometric, Adipokines and Body Fat Distribution with Cortisol

Measures of Adiposity	Cortisol (N=4211)
	Beta (CI)
z-Log-Adiponectin (ng/dL)	0.023 (0.01, 0.036), 0.0005
z-Log-Leptin (ng/dL)	-0.067 (-0.084, -0.05), <.0001
z-Log-Leptin:Adiponectin ratio	-0.051 (-0.065, -0.038), <.0001
z-Waist Circumference (cm)	-0.031 (-0.043, -0.018), <.0001
z-Body Mass Index (kg/m^2)	-0.04 (-0.052, -0.027), <.0001
z-Log-Subcutaneous Adipose Tissue (cm^3) (N=2340)	-0.051 (-0.07, -0.032), <.0001
z-Log-Visceral Adipose Tissue (cm^3) (N=2341)	-0.007 (-0.024, 0.01), 0.4271
z-Liver Attenuation (Hounsfield units) (n=2387)	0.006 (-0.011, 0.022), 0.4988

Adjusted for age, sex, education, occupation, systolic blood pressure, smoking, physical activity, hormone replacement therapy medications, beta-blocker medications and cortisol collect time.

Logged-dependent variable, level-independent: $\%\Delta Y = \left(e^{\beta} - 1\right) * 100$

Interpretations: A 1-SD higher adiponectin is associated with a 2.33% higher morning serum cortisol. A 1-SD higher leptin is associated with a 6.48% lower morning serum cortisol. A 1-SD higher Leptin:Adiponectin ratio is associated with a 4.97% lower morning serum cortisol. A 1-SD higher WC is associated with a 3.05% lower morning serum cortisol. A 1-SD higher BMI is associated with a 3.92% lower morning serum cortisol. A 1-SD higher SAT is associated with a 4.97% lower morning serum cortisol.

Table 4. Categorical Associations of Anthropometric, Adipokine and Body Fat Distribution with Cortisol

Measures of Adiposity	Categories	Cortisol * (n=4211)
		Beta (CI), p-value
Adiponectin (ng/dL)	Q1	ref
	Q2	-0.003 (-0.039, 0.032), 0.8496
	Q3	0.029 (-0.007, 0.065), 0.1091
	Q4	0.055 (0.019, 0.092), 0.0031
Leptin (ng/dL)	Q1	ref
	Q2	-0.079 (-0.118, -0.04), <.0001
	Q3	-0.123(-0.168, -0.078), <.0001
	Q4	-0.168 (-0.214, -0.121), <.0001
Leptin:Adiponectin Ratio	Q1	ref
	Q2	-0.08 (-0.117, -0.046), <.0001
	Q3	-0.11 (-0.147, -0.073), <.0001
	Q4	-0.126 (-0.164, -0.088), <.0001
Waist (cm)	Q1	ref
	Q2	-0.049 (-0.085, -0.014), 0.0109
	Q3	-0.069 (-0.104, -0.034), <.0001
	Q4	-0.09 (-0.126, -0.055), <.0001
BMI (kg/m^2)	1: <25	ref
	2: 25-30	-0.08 (-0.124, -0.045), <.0001
	3: 30+	-0.141 (-0.179, -0.104), <.0001
Subcutaneous Adipose Tissue (Hounsfield units) (n=2340)	Q1	ref
	Q2	-0.037 (-0.09, 0.012), 0.1346
	Q3	-0.107 (-0.157, -0.056), <.0001
	Q4	-0.105 (-0.157, -0.052), 0.0001
Visceral Adipose Tissue (Hounsfield units) (n=2341)	Q1	ref
	Q2	-0.037 (-0.084, 0.010), 0.1252
	Q3	-0.004(-0.05, 0.043), 0.8642
	Q4	-0.015 (-0.063, 0.034), 0.5530
Liver attenuation (Hounsfield units) (n=2387)	Q1	ref
	Q2	0.04 (-0.007, 0.086), 0.0933
	Q3	0.01 (-0.037, 0.056), 0.6848
	Q4	0.023 (-0.023, 0.07), 0.3227

Adjusted for age, sex, education, occupation, systolic blood pressure, smoking, physical activity, hormone replacement therapy medications, beta-blocker medications and cortisol collection time.

Interpretations: $\%\Delta Y = \left(e^{\beta} - 1\right) * 100$

Examples: Adiponectin levels in quartile 4 were associated with a 5.7% higher cortisol than quartile 1. Leptin levels in the 2nd, 3rd, and 4th quartiles were associated with 7.6%, 11.6%, 15.5% lower cortisol (respectively) compared to the 1st quartile. Compared to those with normal BMIs, overweight participants (BMI = 25-29.99 kg/m2) and obese participants (BMI ≥ 30 kg/m2) had 7.7% and 13.2% lower cortisol levels, respectively. Subcutaneous adipose tissue in the 3rd and 4th quartiles had 10.1% and 10.0% lower cortisol, respectively ($p<0.05$).

Figure 1: The Jackson Heart Study Cortisol and Adiposity Cohort

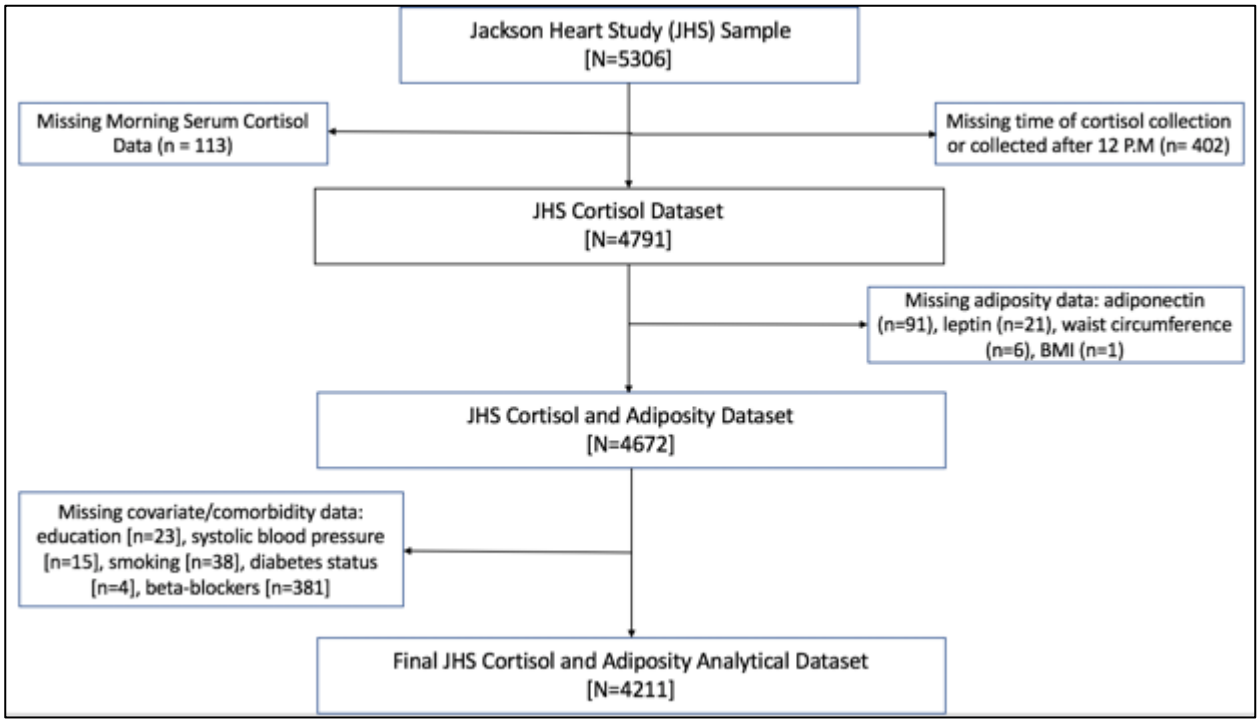


Figure Legend 1:

The Jackson Heart Study cohort included 5,306 participants. Individuals were excluded from the analysis due to missing data on morning serum cortisol (n=113) or on the basis of missing time of cortisol collection/ collection occurring after 12 P.M (n=402). Furthermore, participants were excluded if they had missing outcome or covariate date (adiponectin [n=91], leptin [n=21], waist circumference [n=6], BMI [n=1], education [n=23], systolic blood pressure [n=15], smoking [n=38], diabetes status [n=4], or beta-blockers [n=381].

Figure 2. Summary of Associations between Adiposity Measures and Morning Serum Cortisol

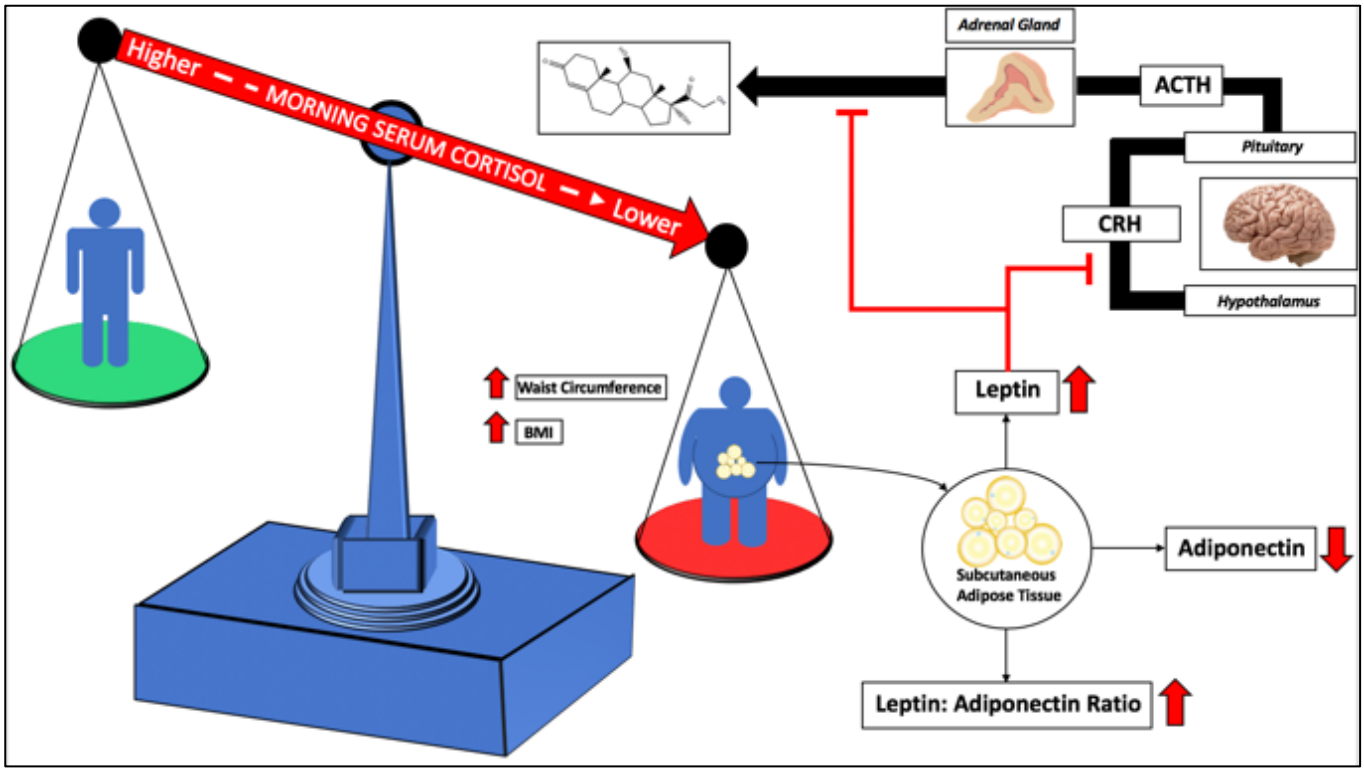


Figure 2 Legend:

Body mass index and waist circumference were negatively associated with morning serum cortisol. The hypothesized mechanism between increasing adiposity and lower cortisol among African Americans involves the preferential storage of adipose tissue in subcutaneous depots. Subcutaneous adipose tissue produces leptin which is able to suppress cortisol production at the hypothalamus and the adrenal gland.

Figure 3. The Relative Magnitude of the Association of Standardized Adiposity Measures with Morning Serum Cortisol

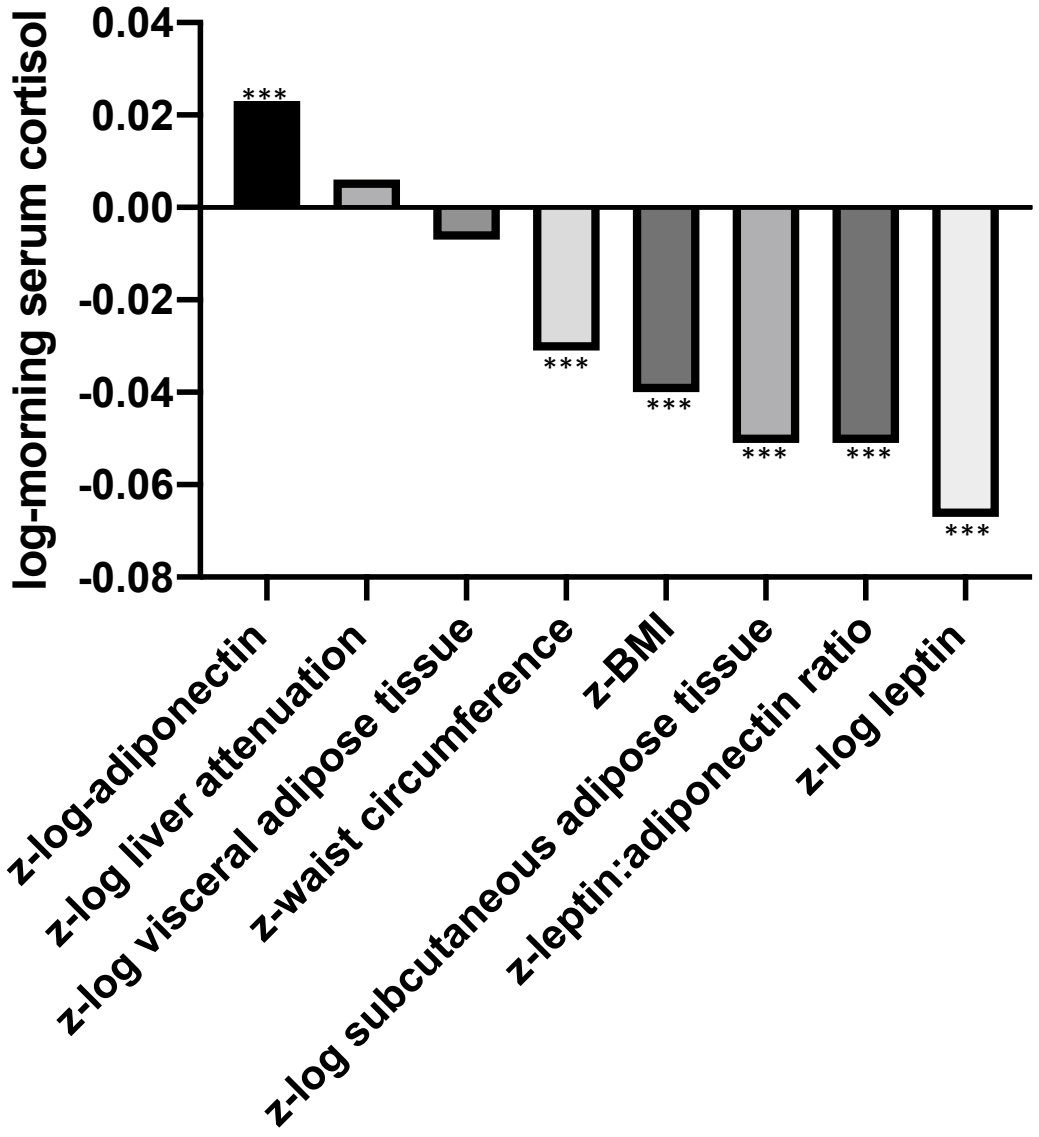
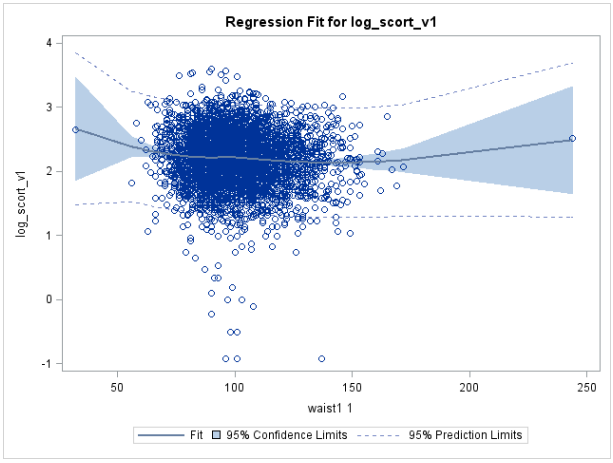


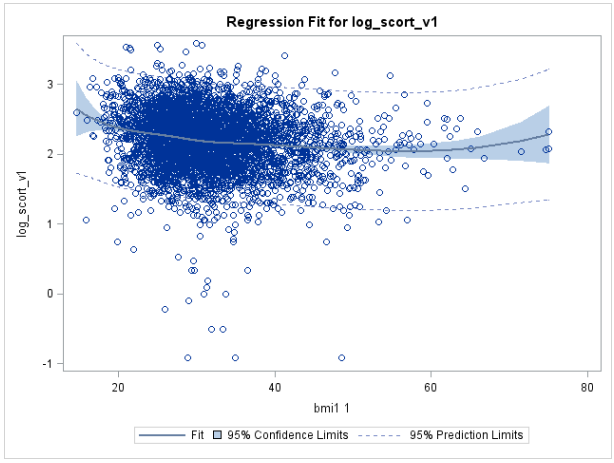
Figure Legend: The relative magnitude of associations of standardized adiposity measures with morning serum cortisol are shown. Leptin had the greatest relative magnitude of association with morning serum cortisol. The data corresponding with the figure is presented in Table 5.

* $p<0.05$, ** $p<0.01$, *** $p<0.001$

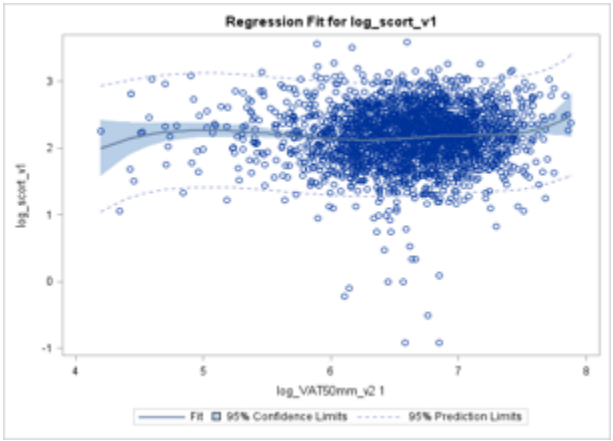
Supplementary Figure 1a.



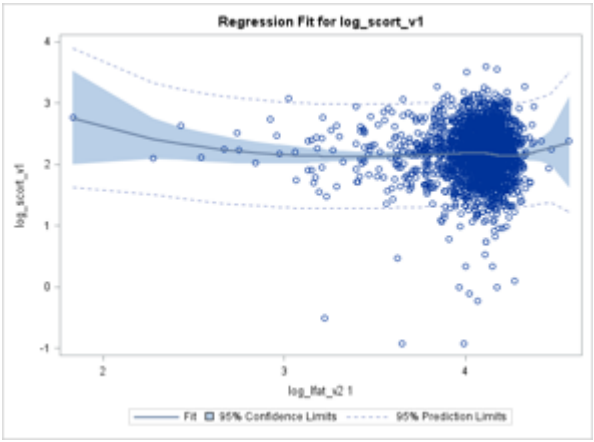
Supplementary Figure 1b.



Supplementary Figure 1c.



Supplementary Figure 1d.



Supplementary Figure 1 Legend:

Supplementary Figure 1a. depicts the fit of the association between log morning serum cortisol and waist circumference. Supplementary Figure 1b. depicts the fit of the association between log morning serum cortisol and body mass index. Supplementary Figure 1c. depicts the fit of the association between log morning serum cortisol and log visceral adipose tissue. Supplementary Figure 1d. depicts the fit of the association between log morning serum cortisol and log liver attenuation. There was no evidence of a non-linear association between log morning serum cortisol and any of the tested measures of adiposity.